## REMARKS

Claims 1, 6, and 17-19 are pending in this application. Claims 1, 6, 17-19 have been rejected. Claims 1, 6, 18, and 19 have been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of these amendments and the following remarks.

**I. Claim rejections under 35 USC §112**

Claims 1 and 17-19 remain rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. It is suggested that because the specification does not describe common identifying characteristics of the genus of polypeptides that bind specifically to BMP-2 and prevent activation of its receptor, that one of skill would not immediately envision such a polypeptide. Applicant respectfully disagrees with this rejection.

As indicated in Applicant's response dated August 10, 2005, BMP-2 and antagonists thereof were well-known in the in the art at the time of filing of the present application, as evidenced by the teachings of Merino et al. (of record) and Hsu et al. (of record). These references, as well as the instant specification (paragraphs [0056]-[0058]), teach that BMP-2 antagonists noggin, chordin, gremlin, cerberus 1 homolog, and DAN bind to BMP-2, thus preventing the interaction of BMP-2 with its receptor. Accordingly, in an earnest effort to facilitate the prosecution of the present invention, Applicant has amended claim 1 to indicate that the antagonistic polypeptide that binds BMP-2 is noggin, chordin, gremlin, cerberus 1 homolog, or DAN. Support for

this amendment is found in paragraphs [0056]-[0058] at pages 17-18 of the specification as filed. Given that these polypeptides are known in the art and further known to antagonize binding of BMP-2 to BMP-2 receptor, one of skill in the art would readily recognize in Applicants disclosure that Applicant was in possession of that which is now claimed. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Claims 1, 6, and 17-19 remain rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. It is suggested that the amount of polypeptide that could be reasonably administered to a patient would not be reasonably expected to prevent BMP-2 receptor activation. It is suggested that the polypeptide to which the claims are directed binds BMP-2, and therefore prevention of BMP-2 receptor activation by the polypeptide is unlikely. The Examiner further suggests that the specification does not exemplify the use of the claimed invention, rather it shows the subcutaneous co-injection of agarose beads coated with recombinant mouse noggin and A549 lung cancer cells reduced growth of the resulting tumor in nude mice. It is also suggested that the art, as evidenced by Tada et al. and Buckley et al. (both of record) teaches that BMP-2 suppresses the transformed phenotype of A549 lung cancer cells and therefore the role of BMP-2 in lung cancer needs to be established to determine whether or not its inhibition would be clinical advantageous. Further, it is suggested that the art in general (*e.g.*, Schuh (2004) *Toxicologic Pathology* 32:53-66; Bibby (2004) *Eur. J. Cancer* 40:852-857; and Peterson et al. (2004) *Eur. J. Cancer* 40:837-844) teaches that there is a common lack of extrapolation of the results of studies performed *in vivo* using

mouse models to accurately and reliably predict the effects of the same treatments of human patients, and therefore Applicant's evidence of the relevance of A549 lung cancer xenograft model is anecdotal at best. The Examiner also suggests that despite the finding disclosed in the instant application that co-injecting mouse noggin and A549 lung cancer cells slows or reduces the formation of tumors in immunocompromised mice, it is disturbing that contacting A549 lung cancer cell line with noggin *in vitro* promotes, rather than inhibits the growth of cells. Further, it is suggested that because the working example shows reducing the growth of lung cancer cells by co-injecting tumor cells and mouse noggin into a mouse, this example does not exemplify the use of the claimed invention, namely a method for treating a pre-established tumor in humans. Applicant respectfully disagrees with this rejection.

As indicated above, the specification at paragraphs [0056]-[0058] teach that BMP-2 antagonists noggin, chordin, gremlin, cerberus 1 homolog, and DAN bind to BMP-2, thereby preventing the interaction of BMP-2 with its receptor. Accordingly, in an earnest effort to clarify the interaction between the antagonistic polypeptide and BMP-2, Applicant has amended the claim to indicate that a therapeutically effective amount of a noggin, chordin, gremlin, cerberus 1 homolog, or DAN polypeptide is administered to antagonize binding of BMP-2 to BMP-2 receptor. Support for this amendment is found in paragraphs [0056]-[0058] at page 17-18 of the specification as filed.

As shown in Figure 14, Applicant has demonstrated that by co-injecting mouse noggin with lung cancer cells, lung tumor growth is reduced, whereas co-injecting BMP-2 with lung cancer

cells results in an increase in lung tumor growth. In light of this disclosure, Applicant respectfully disagrees with the Examiner's suggestion that a role for BMP-2 need be established before the therapeutic benefit of a BMP-2 antagonist can be realized. There is no such requirement for meeting enablement. What is required is that the disclosure, when filed, contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art *to make and use* the claimed invention. MPEP 2164.01. In this regard, Applicant has established that a correlation exists between administration of a BMP-2 antagonist such as noggin and a reduction in tumor growth. Applicant's own publications published in 2003 and 2004 support this finding by showing that *in vivo* lung tumor growth is inhibited by a BMP-2 antagonist.

Moreover, in meeting the enablement requirement, Applicant has used a *bona fide in vivo* animal model for lung cancer and demonstrated that noggin reduces growth of lung tumors *in vivo*. As indicated in Applicant's response filed August 10, 2005, the use of human A549 mouse xenografts for evaluating therapeutic efficacy of drugs for treating lung cancer is well-established in the art as evidenced by the teachings of Sirotnak et al. and Meric et al. (of record). Thus, Applicant has provided an *in vivo* animal model example in the specification, which one of skill in the art would readily recognize as a working example commensurate in scope with the amended claims. MPEP 2164.02 states that if the art is such that *a particular model* is recognized as correlating to *a specific condition*, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.

The Examiner has provided no such evidence for the disclosed *in vivo* animal model. What has been provided is a general commentary on the use of *in vivo* mouse models (*e.g.*, Schuh, Bibby, Peterson), references pertaining to cancers other than lung cancer (*e.g.*, Hardwick, et al., Haramis, et al., Nishanian et al., Ghosh-Choudhury et al., Tomari et al., Nakamura et al., and Wen et al.), and *in vitro* results of BMP-2 suppression of A549 lung cancer cells (*e.g.*, Tada et al. and Buckley et al.). Unlike the teachings of Tada and Buckley, Applicant has placed lung tumor cells under the complex conditions of the *in vivo* environment, wherein the cells are subjected to various growth factors and cell-to-cell contact. Without this *in vivo* context, it is unclear whether the teachings of Tada and Buckley can be held to contradict the instant results.

As indicated, Figure 14 clearly demonstrates that lung tumor growth is statistically significantly reduced *in vivo*, as compared to a control, by administering a BMP-2 antagonist such as noggin. As is well-known in the art, tumors are not static; they continue to grow if left untreated. Accepted treatment regimes include the use of tumoricidal, as well as tumoristatic agents, *e.g.*, Tamoxifen. Accordingly, therapeutic benefit is achieved by reducing the growth of the cancerous cells with tumoristatic agents. Given that Applicant has demonstrated a reduction in growth of tumor cells *in vivo*, treatment has been demonstrated. Moreover, while a mouse noggin polypeptide of SEQ ID NO:2 is exemplified, mouse and human noggin polypeptides share 98% homology (see paragraph [0057] at page 17) and antagonize BMP-2. Thus, one of skill in the art would readily appreciate that whether the BMP-2 antagonist is a human noggin, mouse noggin

or chordin, gremlin, cerberus 1 homolog, or DAN protein, therapeutic benefit is achieved by antagonizing binding of BMP-2 to BMP-2 receptor.

In light of the working examples, claim amendments and accompanying remarks, Applicant respectfully believes that the enablement requirement of 35 U.S.C. 112 is satisfied. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1, 6 and 17-19 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description for reciting "so that BMP-2 receptor activation is prevented." It is suggested that this rejection might be remedied were claim 1 amended to recite, for example, "administering to a patient with lung cancer a therapeutically effective amount of the polypeptide of SEQ ID NO:4 to antagonize binding of BMP-2 to its receptor."

As indicated above, Applicant has amended claim 1 to clarify that a therapeutically effective amount of noggin, chordin, gremlin, cerberus 1 homolog, or DAN polypeptide is—administered to antagonize binding of BMP-2 to BMP-2 receptor. In light of this amendment, it is respectfully requested that this rejection be reconsidered and withdrawn.

**II. Double Patenting**

Claims 1 and 14-19 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 14 of copending Application No. 10/692,824. It is suggested that while the conflicting claims are not identical, they are not patentably

distinct from each other. Applicant respectfully requests that this rejection be held in abeyance until allowable subject matter has been identified in copending Application No. 10/692,824.

**III. Conclusion**

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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